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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/048,346	04/15/93	HUDZIAK R	554C1

BAKER, R EXAMINER

18M2/0414

CAROLYN R. ADLER
GENENTECH INCORPORATED
460 POINT SAN BRUNO BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

ART UNIT	PAPER NUMBER
1814	12

DATE MAILED: 04/14/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☑ Responsive to communication filed on 2/8/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 2, 3, 5, 7, 9-22, 24 & 26 are pending in the application.
   Of the above, claims 9-21 are withdrawn from consideration.
2. ☑ Claims 1, 4, 6, 8, 23, 25 & 27 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 2, 3, 5, 7, 22, 24, & 26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the inventions are not independent, the a search of all groups would not be a burden and a search of the protein would be exhaustive of that for the DNA. This is not found persuasive because the inventions are distinct for reasons of record. Distinct inventions may be restricted even though dependent (MPEP 802.01). With respect to the search burden, the inventions are separately classified and have acquired a separate status in the art as shown by their different classification. In addition, a search of the relevant patent and technical literature would require a search in databases devoted exclusively to nucleic acid sequences for the DNA and amino acid sequences for the proteins.

The requirement is still deemed proper and is therefore made FINAL.

16. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

17. The prior rejection of claims 2 and 24 under 35 U.S.C. § 101 as directed to nonstatutory subject matter is withdrawn.

18. Claims 2, 3, 5, 7, 22, 24, and 26 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

This rejection is maintained from the prior Office action. Applicants arguments have been considered but not deemed persuasive. Applicant has argued that the ligand for HER2 may be isololated and characterized using the the purified extracellular domain of HER2 and cites WO 92/20798 in support of in vitro and in vivo utilities for the ligand. However, WO 92/20798 was published well after the effective filing date of this application and the disclosure therein cannot be used to support utility of the instant claims. The specification in this application fails to teach any of the utilities of the HER2 ligand disclosed in WO 92/20798. With respect to Applicants arguments regarding EP 244,221, even if the extracellular domain may be used to detect and isolate the ligand again the specification fails to establish the utility of the ligand.

Applicant further argues that the receptor is useful for obtaining antibodies which are useful in diagnostic assays. However, in support thereof applicant cites WO 89/06692 which was published after the filing date of the instant application. Again, the disclosure therein cannot be used to support utility of the instant claims. The instant specification is limited to therapeutic utility for antibodies against the receptor and the evidence of record fails to support such a utility for the reasons of record.

19. The following is a quotation of the first paragraph of 35

U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to teach how to make and use the invention ie. failing to provide an enabling disclosure.

This objection is set forth for essentially the reasons discussed above. "If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112." In re Ziegler, 26 USPQ2d 1601. Evidence of utility is required.

The evidence of utility must be commensurate in scope with the claims with respect to the extracellular portion of the HER2 molecule for the reasons of record and those which follow. Applicant has argued that antibodies can be made to peptides having as few as 9 amino acids. Even if this is so, the specification fails to teach any sequences which comprise an epitope displayed by the HER2 receptor or the means and methodology for determining immune epitopes.

Thus, applicants have **not** provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed

invention in a manner reasonably correlated with the scope of the claims broadly including any immunogenic portion of the HER2 extracellular domain. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the portions of the extracellular domain which contain an immune epitope is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986); Amgen, Inc. v. Chugai Phamaceutical Co, Ltd. 927 F.2d 1200, 18 USPQ2d 1016, (Fed. Cir. 1991) at 18 USPQ2d 1026-1027; Ex parte Maizel, 27 USPQ2d 1662 (BPAI, 1993).

Claims 2, 3, 5, 7, 22, 24 and 26 are rejected under and 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

20. The prior rejection under 35 U.S.C. § 112, second paragraph, is withdrawn.

21. The prior rejection under 35 U.S.C. § 112, fourth paragraph, is withdrawn.

22. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

23. Claims 2, 3, 5, 7, and 22-27 are rejected under 35 U.S.C. § 103 as being unpatentable over Yamamoto et al. (AJ) or Coussens et al. (AL) each in view of Weber et al., Dull et al. or Dower et al.

This rejection is maintained from the prior Office action.

Applicants arguments have been considered but not deemed persuasive. Applicant initially argues that the Examiner's position is an "obvious to try" situation. This is not the basis of the rejection. The cited prior art establish clear motivation and a reasonable expectation of obtaining a soluble form of the HER2 receptor. It is not inventive to express a soluble, extracellular portion of a receptor which is known and whose structure is established in the prior art. In this case each of Yamamoto et al. and Coussens et al. teach the complete nucleotide and amino acid sequences for the HER2 (same as c-erbB-2) tyrosine kinase receptor and delineate that region of the receptor which constitutes the extracellular domain (see 1137, first full paragraph of Coussens and Fig. 3B of Yamamoto).

Applicant argues that Coussens and Yamamoto do not suggest a receptor soluble domain but this is suggested by each of the cited secondary references. Each of the references must be considered for what they would have fairly suggested to one of ordinary skill in the art at the time the invention was made. The cited references taken collectively would have suggested the claimed invention to one of ordinary skill in the art familiar with them. The individual references themselves are not required to make a suggestion for the combination to be obvious. As stated in In re Rosselet, 146 USPQ 183 at 186 "the test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would

suggest to those of ordinary skill in the art presumed to be familiar with them." For the purpose of combining references, those references need not explicitly suggest combining teachings. In re Nilssen, 851 F.2d 1401, 7 USPQ2d 1500 (Fed Cir. 1988). Obviousness does not require absolute predictability but only a reasonable expectation of success. In re Clinton, 188 USPQ 365; In re O'Farrell, 7 USPQ 2d 1673.

Applicant argues that the secondary references teach receptor domains which are small than that of HER2 but the claims are not limited to any particlar length and according to applicant may be as small as only 9 amino acids. With respect to Webber, Dull and Dower, these references are merely cited as motivation for expressing the extracellular domain of HER2. Determination of appropriate expression conditions for a given receptor is well within the skill in this art. In addition, the claims are not limited to any particular fragment of the extracellular domain.

The Dull reference is of particular significance in view of Applicants response to the prior Office action. This disclosure is equivalent to that of EP 244,221 discussed on page 4 of Applicants response wherein it is stated that the extracellular domain of HER2 could be fused to a reporter polypeptide for detection of the ligand. Clearly there is a ample motivation and a reasonable expectation of success from the cited prior art, especially Dull et al.

24. Claims 2, 3, 5, 7, 22, 24 and 26 are rejected under 35 U.S.C. § 103 as being unpatentable over Yamamoto et al. (AJ) or Coussens et al. (AL) each in view of Bernards et al. (AR) and further in view of Maddon et al., Hudziak et al (AO), or Masuko et al.

This rejection is also maintained from the prior Office action. Applicants arguments have been considered but not deemed persuasive in overcoming this rejection for the reasons discussed above, in the prior Office action, and those which follow. Applicant argues that Bernards teaches away fromthe invention but this reference is merely cited as teaching expression of the rat neu protein, which is the rat homolog of the human HER2, in a form lacking the majority of the cytoplasmic domain (p. 6854) and that the protein protected animals against tumor cell challenge (Abstract). While the protein of Bernards et al. is not soluble, ie lacking the transmembrane region Maddon et al. is cited as teaching that a soluble receptor may be used as a therapeutic agent or to raise specific antibodies against the soluble portion of the receptor. While the soluble CD4 receptor of Maddon differs from that claimed this reference is simply cited as teaching recognition in the art that soluble forms of known receptors may be used to raise antibodies. As previously discussed, each of Hudziak et al. and Masuko et al. teach the preparation of monoclonal antibodies specifically directed against the extracellular domain of HER2. As such they do not teach away from the invention, contrary to applicants assertion.

25. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to R. Keith Baker whose telephone number is (703) 308-2958.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

KEITH BAKER
PRIMARY EXAMINER
GROUP 1800

R. Keith Baker
April 14, 1994